REMARKS

I. Status of the Claims

Claims 1-15 are pending.

Claims 1, 5, 7, 11, and 13 are amended.

Claim 24 is cancelled.

Claims 16-37 are withdrawn.

II. Interview Summary

An interview was held on October 9, 2007. At the U.S. Patent Office were Examiner Brian S. Kwon; Dr. Joel Bernstein, the inventor; and Richard Lazarus, of Barnes & Thornburg, applicant's representative. Alice O. Martin of Barnes & Thornburg, participated by telephone.

Claims 1-15 were discussed. Prior art used to support rejections under 35 USC § 102 and 103 were publications of Summers, of Kroger, and of Yang. Dr. Bernstein explained why Summers does not anticipate claims 1-9 and 11-15. Amendments are offered to clarify these differences. A discussion also related why Kroger and Yang do not make claims 1-15 obvious.

Also discussed were enablement of "a hepatotoxic compound" and the interpretation of the claim term "consisting essentially of."

Applicant's representatives pointed out that amending from "comprising" to "consisting essentially of" should not require a new search because if anything, the phrase narrows the scope of the claims.

III. Claims are Enabled

The examiner admitted claims 1-9 and 11-12 are enabled.

> for the specific hepatotoxic compound such as acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconozole, divalproex sodium, and valproic acid

Office Action, page 2.

and further to

> one or more of hepatotoxic compound, about 5 mg to about 500 mg of methionine and about 10 mg to 500 mg of nicotinamide

Office Action, page 3.

Yet the examiner objects to a claim term "a hepatotoxic compound."

As discussed during the interview, claim 1 is amended to add "used in treatment of human disease," because that indicates to those of skill in the art, that "hepatotoxic compounds" as those defined as such in the standard texts used by medical practitioners, e.g., the Merck Index, Harrison's Textbook of Medicine (see excerpt in Exhibit A showing relatively small number of hepatotoxic drugs, "Diffuse Hepatocellular Damage"), and the like. Results of clinical trials and drug labels warning of "hepatotoxiciy" remove any need for "undue experimentation" to determine a "hepatotoxic compound" when used in the treatment of human disease.

"Hepatotoxic compound" is a genus and, as the examiner admits, has a large number of species within it, enabled in the present specification. (Office Action, page 4.) Therefore, applicant should be entitled to claim "hepatotoxic compound."

Claim 1 is amended as the examiner suggested during the interview, so "comprising" doesn't follow "consisting essentially of." Claim 13 is amended to specify hepatotoxic compounds.

IV. Summers does not teach all claim elements

Claims 1-9 and 11-15 were rejected under 35 USC §102 (e) by Summers.

Claim 1 was amended to be limited to "consisting essentially of," include only other ingredients disclosed. Please withdraw the rejection based on Summers (see arguments in previous response).

V. A *prima facie* case of obviousness is not established

Claim 1-15 were rejected under 350 USC §103 (e) over Kroger and Yang.

A *prima facie* case of obviousness is not established.

Kroger used nicotinamide and methionine. Mice were injected intaperitoneally with a combination at doses 12.5 mg/kg were said to provide protection. Activities of GOT + GPT were determined in mice to determine if there were hepatoprotective effects.

The examiner admits that

> Kroger differs from the claimed invention in the preparation of a composition comprising acetaminophen, nicotinamide and methionine in the specific amounts, namely about 80-1000 mg dose of acetaminophen, about 5 mg to about 500 mg dose of methionine and about 10 mg to about 500 mg dose of nicotinamide, per standard dose.

There are three critical aspects of the pending claims which are not taught by the Kroger Papers:

a. Route of administration – In the Kroger Papers, nictinamide or methionine or their combination are administered intaperitoneally ("IP"). This is a very substantive difference from the routes of administration claimed in the '760 application. First, IP is virtually never used in humans [1,2] for two principal reasons: (a) IP provides significantly faster and more substantial blood levels of drugs [1,3] than other routes of administration. (b) risk of infection and local adhesions are unwarranted for use of this route in humans [1] . There are no drugs approved for IP administration to humans in North America or Europe.

b. Composition and Method – In the Kroger Papers, nictinamide and/or methinonine are administered as separate IP injections and the acetaminophen and methotrexate are administered orally or by IP respectively at an earlier time point. In contrast, the compositions cited in the '760 application, all components (the hepatotoxic active drug agent and the hepatoprotective agents, nictinamide, methionine, and folic acid) are provided in the same dosage form and administered together in this dosage form (e.g. capsule, tablet, solution).

c. The dosages of nicotinamide and methionine administered IP for protective effects in the Kroger papers are very substantially greater then those in the '760 application. IP dosages in the Kroger Papers range from 25-100 mg/kg nicotinamide and 50-300 mg/kg methionine when each is given alone, to 12.5 mg/kg of each when they are both administered in separate IP injections. Based on the average body weight for adult Americans [4] the dosage of nicotinamide in the claims of the '760 application ranges from .11 mg/kg to 5.7 mg/kg for males and from .13 mg/kg to 6.7 mg/kg for females, and the dosage of methionine in claims

of the '760 application ranges from .29 mg/kg to 5.7 mg/kg for males and from .33 mg/kg to 6.7 mg/kg for females. IP injection results in much higher and much faster peak blood levels of drug. In the '760 application, these dosages are provided orally or by injection **not into** the peritoneum. Consequently, the dosages of nicotinamide and methionine in present claims are minuscule compared to the Kroger papers.

The discussion of these differences renders it clear that the Kroger papers do not teach that much lower dosages of nicotinamide and methionine, administered in a single dosage from with a hepatotoxic drug (e.g. capsule, tablet, solution), given by completely different routes of administration than Kroger, would provide safe and effective hepatoprotection from a hepatotoxic drug.

In addition, Table 5, P. 205 of H. Kröger et al. General Pharmacology 33:203-206, 1999 demonstrates that administering 50 mg/kg of nicotinamide intraperitoneally to mice along with 50 mg/kg methotrexate and 50 mg/kg acetaminophen produced significantly higher GOT and GPT elevations (increased liver toxicity) versus mice receiving 50 mg/kg methotrexate plus 50 mg/kg acetaminophen alone. Additionally, this Table demonstrates that higher doses of nicotinamide (i.e. 100 mg/kg and 250 mg/kg) given to the mice in conjunction with methotrexate and acetaminophen, while not increasing liver toxicity as did 50 mg/kg of nicotinamide, nonetheless provided no protection against combined methotrexate/acetaminophen-induced liver toxicity. Consequently, Kröger teaches that nicotinamide is non-hepatoprotective at high nicotinamide dosages, and at lower nicotinamide dosages, nicotinamide increases liver damage from methotrexate and acetaminophen. Consequently, Kröger teaches the direct opposite of the 760 application regarding nicotinamide's protective effects.

The '757 patent (Yang) claims a method and compositions of treating acetaminophen overdose by administering an agent comprising diallyl sulfide within about 6-24 hours after an overdose of acetaminophen has been ingested. It further provides that N-acetyl cysteine, L-methionine, L-cysteine (compounds with sulfhydryl groups) and mixtures thereof can be added to the diallyl sulfide if desired. Yang taught sulfhydryl.

In contrast, the present application teaches compositions that contain acetaminophen and mixtures of nicotinamide and methionine, or acetaminophen and mixtures of nicotinamide,

methionine and folic acid. The '757 patent neither teaches nor claims any combination or formulation of these agents and acetaminophen. The composition and method claims of the '757 patent require diallyl sulfide. In contrast, the present application neither teaches nor claims diallyl sulfone. Furthermore, the '757 patent's teachings are for compositions containing solely agents which "supply sulfhydryl groups." Neither nicotinamide nor folic acid contains a sulfhydryl group in the molecules.

To properly combine two references to reach a conclusion of obviousness, there must be some teaching, suggestion or inference in either or both of the references, or knowledge generally available to one skilled in the art, which would have led one to combine the relevant teachings of the two references. *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc. et al.* 776 F. 2d 281, (CAFC 1985), Both the suggestion to make the claimed composition or device or carry out the claimed process and the reasonable expectation of success must be founded in the prior art, not in applicant's disclosure. *In re Vaeck* 947 F. 2d 488, (CAFC 1991). Citing references which merely indicate that isolated elements and/or features recited in the claims are known is not a sufficient basis for concluding that the combination of claimed elements would have been obvious, *Ex parte Hiyamizu* 10 PQ. 2d 1393 (BPAI 1988), absent evidence of a motivating force which would impel persons skilled in the art to do what applicant has done. *Ex parte Levengood* 28 PQ. 2d 1300 (BPAI 1993). The references, viewed by themselves and not in retrospect, must suggest doing what applicant has done. *In re Shaffer* 229 F. 2d 476 (CCPA 1956). Obviousness requires a suggestion of all limitations in a claim ". *CFMT, Inc. v. Yieldup Int'l Corp.*, 2003 U.S. App. LEXIS 23072 (Fed. Cir. 2003). One cannot simply backtrack from the invention to find a connection to the prior art. Hindsight must be avoided. *W.L. Gore and Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983). To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998).

No other fees are believed due at this time, however, please charge any deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (41959-102739).

Respectfully submitted,

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